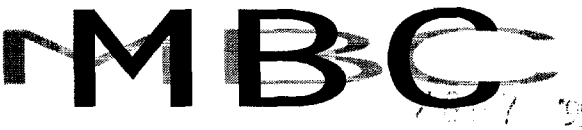

Massachusetts Biotechnology Council



# An Assessment of FDA Modernization and FDAMA Implementation

**Submitted by the**
**Massachusetts Biotechnology Council**

**FDA External Stakeholders Meeting**
**Boston University Medical Center**
**April 28, 1999**

**Docket Number 99N-0386**
**(Submitted May 14, 1999)**

**Date:** May 14, 1999

**To:** Food and Drug Administration, HHS
Dockets Management Branch (HFA-305)

**From:** Massachusetts Biotechnology Council (MBC)

**Re:** "Talking With Stakeholders About FDA Modernization" –
Comments Solicited By FDA For Docket Number 99N-0386

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## INTRODUCTION

The Massachusetts Biotechnology Council (MBC), a not-for-profit trade association representing 250 companies engaged in biotechnology research, development, manufacturing, and support services, is pleased to participate in ongoing dialogue with the Food and Drug Administration. The impetus for enhanced industry-agency interaction and consultation has its statutory basis in the Food and Drug Administration Modernization Act of 1997, as set forth in Section 406(b). In addition, and just as important, the Massachusetts Biotechnology Council is compelled by ideals of good corporate citizenship to uphold the spirit as well as the letter of Section 406(b) by engaging the FDA in a proactive, constructive manner throughout the course of FDAMA implementation and FDA modernization.

The MBC's participation in the April 28, 1999 external stakeholders meeting held in Boston continued a precedent of active involvement in the FDA's Section 406(b) outreach mission. On July 18, 1998, the MBC published and released a comprehensive report detailing recommendations for FDAMA implementation and regulation, a document that has come to be known as the "FDAMA White Paper." Subsequently, an MBC delegation met with senior staff from Senator Edward M. Kennedy's office and FDA Office of Policy Director William B. Schultz on November 30, 1998 to discuss FDAMA White Paper recommendations. And on April 1, 1999, MBC board members were able to meet personally with FDA Commissioner Dr. Jane Henney and Senator Kennedy for a ninety-minute discussion of relevant substantive issues.

The present document was prepared expressly for the April 28 stakeholders meeting. In compiling this paper – which also served as an organizing platform for the MBC's oral presentation – its authors sought to build on earlier communications designed for FDA consumption as well as take a prospective look "over the horizon" at new issues set forth by the FDA. In doing so, we endeavored to meet what in our estimation were dual purposes of the April 28 meeting: 1), to discuss FDAMA implementation and specific performance targets (as so described on the FDAMA web site); and 2), to offer industry recommendations on how the FDA can strengthen its science base and improve its communications processes (as outlined in the Federal Register, March 22, 1999).

Accordingly, this paper is essentially in two parts. First, we address the call for input on science base/communications processes strategies by responding to the five related questions as listed in the March 22 Federal Register, with topics of the FDA's science base and risk/benefits processes particularly highlighted. Second, we offer an assessment of and solicit agency comment on FDAMA implementation. In addition, there is commentary and query on an outstanding issue of concern to the MBC regarding generic biologics.

# *I. FDA MODERNIZATION*

## A. IMPROVING THE SCIENCE

**Issue:**

In a time of unprecedented scientific advances and breakthroughs, the FDA is seeking to develop a capacity to access state-of-the-art science at all times. The Agency recognizes that its decisions require this heightened scientific capacity especially in light of an "avalanche of new information from government, academic, and industry scientists." Furthermore, the FDA has solicited proposals from stakeholders on how best to facilitate the exchange and integration of scientific information so that the FDA can meet its public health responsibilities.

**Background:**

The Massachusetts Biotechnology Council has set a precedent working with the FDA to improve processes in a manner that is mutually beneficial to industry and the Agency. Together with the district office of FDA, the MBC developed a model program for pilot pre-inspection approvals that won both entities Vice President Al Gore's Hammer Award for helping to "reinvent government." The MBC proposes to build on that precedent and relationship with the Agency by developing a model program whereby FDA reviewers can gain exposure to new, cutting edge technologies. At the same time, the MBC suggests that the FDA produce seminars that will assist companies in making their dealings with the Agency more efficient.

**Discussion and Proposed Action:**

As one way to help the FDA build on its science base, the MBC proposes that it help develop seminars designed for FDA reviewers that will assist them in maintaining a high level of technological and scientific expertise. These seminars would include presentations by academia and industry. It is further proposed that the FDA reviewer seminars be held at some "neutral" location, such as at the University of Massachusetts Biologics Laboratory in Boston (this laboratory is a CDC alternative site and has previously accommodated FDA training sessions). To facilitate this proposal, or at least to begin exploring its feasibility, the MBC requests that the FDA designate a contact – either at Rockville or at the District Office – through which we can initiate a dialogue on this topic.

As an additional way to enhance the working relationship between Agency and sponsors, the MBC proposes that the FDA conduct its own set of guidance seminars whose purposes would include letting companies know how to improve reporting, interaction, and discussions with the FDA.

## B. THE ROLE OF SCIENCE ADVISORY PANELS

**Issue/Background:**

Advisory panels provide the FDA with a third party mechanism for evaluating complex and controversial scientific matters. Theoretically, expert advisers add to the FDA's understanding of difficult issues, and thereby enhance the Agency's science base. But the very nature of the panels and the role they play in the FDA approval process have come into question, to the point where there is a crisis of confidence in the advisory panel system. There is widespread belief that the advisory panels are being utilized too frequently, and that they are functioning more as endorsers of FDA positions rather than as objective third party evaluators. In addition, the advisory panels' negative impact on companies' stock prices (even when product is recommended for approval) and ability to raise research dollars is a major concern to industry.

**Discussion and Proposed Action:**

In order for the FDA to utilize the Advisory Panels in a more focused, and less frequent fashion, the MBC recommends the following:

1. If the review of a biologic or new drug is progressing through the FDA in a satisfactory manner and the company has demonstrated the necessary efficacy and safety, the MBC recommends the FDA move directly to rapid approval rather than an Advisory Panel meeting.

2. Occasionally, a sponsor might want advisory committee input during the drug development process, especially when there are different ideas regarding clinical end points or statistical plans for demonstrating clinical benefit. Advisory Committees may be useful in making recommendations in framing an appropriate clinical protocol or development of a statistical plan.

3. The MBC recommends that a "best practice" be established to improve on the consistency of the advisory committee function. Such best practices could include sponsor participation in the development of the meeting agenda and sponsors given ample notice to prepare and supply additional materials for the meeting. The recent standard operating procedures outlined in the guidance document "Guidance on Amended Procedures for Advisory Panel Meetings" January 26, 1999 should be adopted for all CBER and CDER advisory committee meetings. The FDA should also change section I.B.4 to allow that substantial information on the effectiveness or safety of the product, available to the FDA after the initial panel package has been distributed, be provided to the panel and sponsor as a panel package addendum.

4. Additionally, CBER forwards the FDA comments and package to the sponsors prior to the advisory Panel meeting. This allows the sponsor to clarify any questions directly to the reviewer prior to the meeting. The advisory panel can then focus their valuable time on the remaining unresolved issues. However, CDER does not follow such a procedure. Harmonization between the two centers utilizing the best practice of CBER would be recommended.

## C. RISKS AND BENEFITS

**Issue:**

Most products in the American marketplace, especially medical ones, have two facets. On one side they benefit users and often improve lives. They are, however, without risk and their use can result in known and unknown side effects. Consumers must weigh benefits and risks before using these products, oftentimes with incomplete information. In order to address this issue, the Food and Drug Administration has asked for responses to the question: "What actions do you propose for educating the public about the concept of balancing risks against benefits in public health decision-making?"

**Background:**

FDA's mission is to promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner. Under FDA's Plan for Statutory Compliance (November 1998) addressing the requirements set forth in Section 406 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), several objectives were stated, including:

a. Maximizing the availability and clarity of information for consumers and patients regarding new products;
b. Implementing inspections and postmarket monitoring; and
c. Ensuring FDA's access to scientific and technical expertise.

**Discussion and Proposed Actions:**

The ability to improve public education and understanding about the concepts of balancing risks against benefits in the public health decision-making process could be enhanced with several new or expanded concepts developed and implemented by the FDA, sponsors, patient groups, and other governmental agencies.

1. The concepts of risk / benefit analyses should be expanded in discussions and agreements between the FDA and sponsors throughout the development process. FDAMA has provided a guideline for the management of meetings between sponsors and FDA and the Massachusetts Biotechnology Council in its White Paper of July 18, 1998 provided Points to Consider relative to Section 119 of FDAMA (Content and Review of Applications: Meetings). In accordance with proposals made in that document, risk / benefit analyses should be documented and agreed upon during each critical meeting. Donna Shalala, Secretary for

Health and Human Services, in her letters to Congress of November 1997 regarding PDUFA Reauthorization Performance Goals and Procedures stipulated that FDA will agree upon the design, execution, and analyses of protocol(s) that will form the primary basis of efficacy for approval. In the same manner, the FDA and sponsors should also discuss criteria and develop agreements that will form the basis for acceptable risk of the product for approval. Furthermore, if a product is to be discussed at a public Advisory Committee meeting as part of the approval process, a summary of the FDA and sponsor agreements regarding risk / benefits of the drug which have occurred during the development / review process as well as the final position should be presented as part of the balanced review process.

2. The agency's criteria for presenting well-balanced information to the consumer need to incorporate all aspects of the health care system. Risk / benefit information is provided in the Package Inserts which accompany distribution of prescription products, is associated with ads for prescription products, and a Patient Package Insert often is provided when prescription products are dispensed. Because of the complex nature of this information and a general lack of public knowledge regarding the development process, this information is often not read, overlooked or mis-interpreted if read. While other forms of information communication are available (web-sites, etc.), the same information is only being provided in a different manner. In order to address this concern, we would propose that FDA explore pilot programs for effective education regarding risk / benefits of prescription products with the primary public contact persons – i.e. prescribing physicians or dispensing pharmacists. These are the individuals with background and training to understand the risk / benefits and who can directly assure that patients best understand the risks / benefits of the products. This type of pilot program would be most beneficial for "fast track" products. FDA's "Pharmacist Education Outreach Program" should be expanded. In today's managed care health system, it is likely that insufficient time is allotted or allowable for this purpose. Thus, a cooperative agreement must be reached between all parties in the health care system (biologic sponsors, FDA, physicians / pharmacists, and health-care payers) which supports physicians / pharmacists in providing simplified information to patients. Collaborations with all "stakeholders" – i.e. media, consumers, patient groups, and other federal agencies – are encouraged to assure that the diverse needs of different patient populations are met.

3. The timely dissemination of current and cutting edge "scientifically sound" information regarding potentially new uses and findings of drugs and biologics should be expanded. This includes the dissemination of information on unapproved / new uses and timely information regarding post-marketing surveillance of new and existing products. FDA and sponsors need to work cooperatively to develop the full potential of the Internet as a two-way communication tool as part of this process. Information regarding new approved and "scientifically sound" information on unapproved uses should be readily

available to consumers and health-care professionals in an effective manner. In a similar manner, safety profiles and updated safety information regarding products should also be readily available via the Internet. Information from the FDA's Adverse Events Reporting System (AERS) should be promptly posted on the Internet as a part of this process.

4. The FDA in order to communicate effectively with consumers and patients, needs to enhance and expand the agency's collaborations with industry, other government agencies, academia, and patient groups. In this manner, information exchange, scientific expertise, and important interchanges regarding key information, including risk – benefit analyses, can occur. FDA should enhance its collaborations particularly with the NIH regarding providing science-based expertise and patient education.

## D. ADDITIONAL SPECIFIC COMMENTARY: Strengthening the Science Base/Improving Communications Five Questions/Five Responses[1]

### 1. Risk-based Decision Making

*Issue*: Science based decisions are made throughout the life span of products from initial research, development and testing, through production, marketing, and consumption. These decisions require the best science to identify, evaluate, and balance product risks and benefits. It is crucial that FDA, in collaboration with product sponsors, develop a shared understanding of new science and technologies and their effect throughout a product's life span.

*Question*: What actions should the FDA take to expand its capability to incorporate state-of-the-art science into its risk-based decision making?

*Response*: The Massachusetts Biotechnology Council (MBC) supports FDA's ability to make science-based regulatory decisions in a timely manner for innovative new products. We would propose that for FDA staff to acquire the best science to identify, evaluate, and balance product risks and benefits the following be considered.

FDA should expand the use of its "workshop" programs for new technologies and products to gather the best scientific information on product / technology risks and benefits concurrent with product review. An objective of each "workshop" would be to have a "state-of-the-art" summary of the proven /potential benefits of new products / technologies as well as the risks associated with implementation.

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[1] Federal Register Notice dated 22 March 1999 announcing the 28 April 1999 "Stakeholders" meeting.

Where possible, all parties participating in the workshop, including public or consumer interest groups, should be invited to propose risk and benefit criteria for acceptance of the new product or class of products. Priority scheduling for "workshops" should be given to products that qualify for "fast track" status. The impact of new technologies, if implemented at a future post-approval time frame, on the overall risk-benefit profile should be considered.

FDA, as part of the FDAMA meetings scheduled with sponsors for product approval, should continue to work cooperatively to establish agreements on the acceptability of the risk criteria as well as benefit criteria for product approval at the earliest development stage, but no later than the End of Phase II meeting.

**Additional Items for Consideration**

- Submit a detailed product development plan (PDP) to the FDA as early as possible, preferably at the pre-IND stage.
- System for defining new product risks and dealing with the level of risk as new information becomes available over time.
- Go to the experts, the research institutions and companies leading the development of a new technology. For general details hold a public forum. For specific details on how a new technology applies to a specific product, approach the product's sponsor.
- Workshops on general topics related to specific areas of science sponsored by the FDA or trade organization.
- Seminars on a new technology for FDA personnel presented by new drug sponsors. These would be intended for FDA personnel in specific review divisions.
- Utilize other government organizations, such as the NIH, as technical resources.
- FDAMA section 408 and 409 education, training and technical awareness.
- Early development and frequent updates to the following documents would be helpful in the risk assessment process:
  -Investigator's brochure updates related to benefit/risk.
  -Summary of benefit to risk needed for NDA/BLA.

**2. FDA Capacity for Information Exchange and Integration**

*Issue*: As the FDA attempts to meet its public health responsibilities, the speed of discovery results in an avalanche of new information from government, academic, and industry scientists.

*Question*: What actions should the FDA take to facilitate the exchange and integration of scientific information to better enable the agency to meet its public health responsibilities throughout a product's life cycle?

*Response*: Essential to the timely review and approval of new products as well as effective monitoring of already approved products is the compilation and review of

scientific and clinical data from numerous sources. We are at the start of an age where Internet communications allow for the rapid ability to transmit and compile information quickly. Its use must be controlled and organized though to avoid an information "nightmare" which is overloaded or not useful for its intended purpose.

We propose that the FDA and sponsors of new drugs explore the feasibility of a pilot program for establishing "web sites" on new products which would be used as interchange forums for scientific information. Certain parts of the product web site would have restricted access to facilitate exchange of confidential information between a sponsor and the FDA. Other parts of the web site would serve as a reference for available reference information. It is recognized that many details of the information which could be collected as well as how it is administered would need to be worked out prior to initiation of a pilot program.

Additionally, it is recognized that sponsors often have the most current scientific knowledge regarding new technologies or products. It is proposed that the FDA and sponsors, through trade organizations like the MBC, establish twice-yearly training sessions in new technologies or product categories. A joint organizing group of industry and FDA divisions would establish the program for these training sessions. In most cases, the training sessions would be restricted to FDA personnel and the sponsors providing the training, so as to encourage meaningful dialogue.

**Additional Items for Consideration**

- Improve skills and understanding related to knowledge management and dissemination within FDA.
- FDA needs individuals skilled in collaborative management and working at a level with the authority to cross-divisional and corporate boundaries.
- Periodic updates from sponsor to the FDA on new scientific developments specific to their development candidate, in summary format, with further details provided upon request.
- User friendly integrated software systems to manage avalanche of new information.
- Efficient daily or weekly news service targeted at FDA personnel for specified topics i.e., review of specific new drug, general update on new science/finding. Non-commercial, all summary format, predigested an on personnel desk when they arrive in the morning.
- Develop simple systems to measure the effectiveness of communication initiatives.

**3. Public Education - Risks and Benefits**

*(As part of its oral presentation at the April 28 stakeholders meeting, the MBC delegation offered an expanded discourse on risk/benefit and public education, or Question # 3 in the Federal Register. Those comments appear on pages 7 – 9. Additional suggestions from MBC members responding to Question # 3 are noted below.)*

**Additional Items for Consideration**

- Include information on risk/benefit concept in the clinical trial database being developed by NIH under FDAMA section 113.
- Promote series of awareness articles in national publications (newspapers and magazines) and possible NOVA educational TV series.
- Continue efforts to provide risk/benefit information through the FDA web site.

**4. FDA Resource Allocation**

*Issue*: The agency stated in the "FDA Plan for Statutory Compliance" that inflation has eroded real assets that can be applied to meet its public health mission while Congress has increased its responsibilities. As a result, the FDA must allocate its limited resources to achieve the greatest impact.

*Question*: What actions should be taken to enable the FDA and its product centers to focus resources on areas of greatest risk to the public health?

*Response*: The MBC and individual industry members are aware of the limited resources available to the FDA to meet its responsibilities. Resource allocation is an ongoing process that must be capable of adjusting to changing while addressing its public health mandates. The following items are offered for FDA's consideration:

**Items for Consideration**

- Assess and improve resource allocation decision techniques to enhance:
  - -FDA credibility and public trust
  - -Quality of information to base decisions upon
- Enhance creativity and innovation
- Flexible organization accepting change.
- Organization designed for speed and decision making.
- Identify the innovators and create a purpose or mission for project groups.
- Shift responsibilities for selected items to third parties or other government organizations.
- Re-engineer application review process to allow third party review support.
- Continue to standardize data presentation standards and format.

**5. FDAMA Communication Process**

*Issue*: FDAMA requires the agency to continue to meet with stakeholders on key issues. Meetings have ranged from explaining the positions of the agency on particular issues to working with sponsors on product applications. Historically, these interactions have benefited both stakeholders, through better knowledge of FDA, and the agency, by leading to positive changes in its operations. The agency wants to assure that its stakeholders are aware of and participate in its modernization activities.

*Question*: What additional actions should be taken to enhance the communication processes that will allow for ongoing feedback and/or evaluation of our modernization efforts?

*Response*: As proposed by the MBC in its "White Paper", we believe that additions/clarifications to the provisions of FDAMA would allow our industry to make breakthrough products more available to patients in a time-sensitive manner as well as allow FDA to plan work-flow requirements for product review.

During the first quarter of 1998 representatives from several of the MBC's Member Companies formed a Working Group to collectively identify concerns with the FDA review and approval process and to propose improvements during FDAMA implementation. The Working Group met over several months and identified specific priority issue areas: (1) performance goals, user fees, and meetings; (2) manufacturing issues; (3) fast track; (4) off-label uses; and (5) pharmacoeconomics. These areas became the focus for the work of subgroups, and their work product then was reviewed by the full Working Group and, ultimately, by other Member Companies and the MBC Board of Directors. The "White Paper" was completed and submitted to the FDA July 18, 1998.

The MBC recognizes that, through collaboration, the general public, FDA, and industry may realize the most fundamental objective of FDAMA-- the "prompt approval of safe and effective new drugs and other therapies ... so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease." The MBC urges the FDA to continue to consider the MBC FDAMA Working Group as a resource. The following items are offered for FDA's consideration:

**Items for Consideration**

- Ongoing written dialogue, and/or meetings with trade organizations such as the MBC, RAPS and BIO to address concerns/questions from individual companies on FDAMA issues.
- FDAMA needs to be recognized by all parties involved as an ongoing and extended process.
- Shift a portion of the FDA reporting task to independent committees or to trade organizations such as the MBC.
- Early collaboration between FDA and industry in developing guidelines.
- Continue to support articles in trade publications and meeting presentations on the status of FDAMA.

## *II. FDAMA IMPLEMENTATION*

On July 17, 1998, the MBC submitted for review and comment by the FDA a FDAMA "White Paper." This document outlined a number of FDAMA implementation issue areas and suggested numerous ways the FDA could expedite the legislation's goals speedily and efficiently. The following section continues the discussion of some FDAMA White

Paper points that remain outstanding. Also included in the following commentary is a discussion of generic biologics, an issue which, though not a formal part of the recent White Paper document, remains of concern to the MBC to the extent that the organization feels compelled to raise the topic with the FDA whenever the opportunity arises.

## A. FAST TRACK PRODUCTS

**Issue:**

The "fast track" provision of FDAMA requires, among other things, that FDA "establish a program to encourage the development of surrogate endpoints that are reasonably likely to predict clinical benefit for serious or life-threatening conditions for which there exist significant unmet medical needs."[2] To date, FDA has neither established nor proposed establishing such a program. As a result, there is little or no guidance to either industry or Agency personnel as to how sponsors can demonstrate that proposed surrogate and/or short-term clinical endpoints are "reasonably likely" to predict clinical benefit for purposes of accelerated approval (in diseases other than cancer and AIDS). The industry proposes that the Agency initiate the program required by law by developing a guidance document on this issue and offers its cooperation and assistance in preparing such a document.

**Background:**

In 1992, FDA promulgated its "accelerated approval" regulations, which recognize that development of important new therapies for serious or life-threatening diseases requires greater regulatory flexibility than would be appropriate for treatments that are intended for use in less serious diseases or which appear to offer little or no therapeutic benefit over existing treatments. Under these regulations, an "accelerated approval" may be granted if a clinical trial demonstrates an effect on an unvalidated surrogate endpoint that is "reasonably likely" to predict clinical benefit. Accelerated approval is granted on the condition that the surrogate be validated through a post-approval study demonstrating actual reduction in morbidity or mortality, and provides for expedited procedures for the withdrawal of such approval should such studies fail to prove ultimate clinical benefit.

Among the most important provisions of the FDA Modernization Act (FDAMA) is the creation of a "fast track" program to codify and expand upon these principles. In 1998, FDA published its "fast track" guidance document, as required by FDAMA. This guidance document has been generally well received by both the biotech and pharmaceutical industries, but it does not fully address several important issues raised by the "fast track" program, including the statutory requirement that FDA "establish a program to encourage the development of surrogate endpoints that are reasonably likely to predict clinical benefit for serious or life-threatening conditions for which there exist significant unmet medical needs."

[2] See section 506(b)(2) of the Food, Drug and Cosmetic Act.

**Discussion:**

The following issues are those for which a discussion should be initiated between the industry and the Agency, leading to a points-to-consider document that facilitates agreements as to whether a proposed surrogate or short-term clinical endpoint is "reasonably likely to predict clinical benefit" and, therefore, can result in accelerated approval under "fast track."

- Is it possible to describe the quantity and quality of data that demonstrate a sufficient correlation between a surrogate endpoint and the expected clinical outcome to conclude that the former is "reasonably likely" to predict the latter?

- FDA's "fast track" guidance document recognizes that short-term clinical endpoints may serve as the basis for an accelerated approval, so that longer-term data may be collected on a post-approval basis. What steps is FDA taking to ensure that this principal is being applied consistently across Centers, Offices, and Divisions?

- How can the development and approval of "ultra-orphan" drugs be facilitated, given the limited data with respect to both historical controls and biochemical markers/surrogate endpoints?

- In cases where a primary surrogate endpoint has been met, how useful is it to show corollary trends in secondary endpoints that measure short-term clinical benefit as a means of increasing the probability that the primary surrogate endpoint is indeed predictive of clinical benefit?

- What can be done to ensure that health plans respect FDA's determination that a product is safe and effective, and no longer investigational, in cases where the product has received an accelerated approval and the required Phase IV (post-approval) study is still ongoing?

## B. PEDIATRIC STUDY PROVISIONS

**Issue:**

"Biological products" are ineligible for orphan drug market exclusivity extensions under FDAMA's pediatric study provision.

**Background:**

Orphan drug market exclusivity is available to both "drugs" and "biological products."[3] However, FDAMA's pediatric study provision – which provides for extensions of this and other forms of market exclusivity under certain conditions – applies only to

[3] *See* the Orphan Drug Act, which appears at section 526 *et seq.* of the FDC Act.

"drugs."[4] Since orphan drug exclusivity is the only type of market exclusivity that applies equally to both drugs and biologics, it is appropriate for pediatric extensions of such exclusivity to also apply equally to both types of products.

**Discussion:**

Under current law, if two companies are developing different products for the *same* rare disease -- one regulated as a drug and the other as a biologic -- only the company developing the drug will be eligible for a pediatric extension. Yet if the drug product is likely to be used in children with a rare disease, so is the biological product for the same disease. Indeed, FDA lists both drugs and biologics in its "pediatric study priority" list, and indicates in a new rule that the Agency expects that such studies will be routinely performed for many future drugs and biologics.[5] Given the burden that such studies will place on the small biotech companies who are the typical developers of biological products for rare diseases, it is fair and appropriate for Congress to provide that the companies developing such products be made eligible to receive the same incentives/benefits as are already provided to the those developing drugs for rare diseases.

**Proposal:**

FDA should urge Congress to amend FDAMA's pediatric study provision (section 505A of the Federal Food, Drug and Cosmetic Act) so that "biological products" are eligible for orphan drug market exclusivity extensions under the same conditions as apply to "drugs." The biotech industry proposes that the law be amended to create an incentive (or reward) for the sponsors who conduct FDA-requested (or –required) pediatric studies on biological products designated for the treatment of rare under the same circumstances as are currently provided with respect to drugs in section 505A.[6]

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[4] The pediatric study provision provides a mechanism by which a sponsor who performs an FDA-requested pediatric study on a "drug" that is, or will be, approved under section 505(b) of the FDC Act, is eligible for a 6 month extension of any unexpired market exclusivity. Three types of market exclusivity are eligible for extension:
(a) Hatch-Waxman market exclusivity periods, during which ANDAs may not be approved;
(b) patent term market exclusivity periods, during which ANDAs may not be approved; and
(c) orphan drug market exclusivity periods, during which neither NDAs or ANDAs may be approved.
Since "biological products" are approved under section 351 of the Public Health Service Act, and not under section 505(b), such products are ineligible for pediatric market exclusivity extensions under current law. This makes sense with respect to Hatch-Waxman and patent term exclusivity: these forms of exclusivity apply only to drugs and merely bar approval of generic products during the exclusivity period. But since drugs and biologics are *both* eligible for orphan drug market exclusivity, orphan exclusivity should be extendible for both.

[5] A recently promulgated regulation suggests that FDA will routinely require pediatric studies to be performed for new products. Under FDAMA, any such requirement for a pediatric study will be treated as a "request" for which an exclusivity extension may be granted -- provided the product is regulated as a "drug."

[6] Since biological products are not eligible for Hatch-Waxman-type market exclusivity, nor are they approvable on the basis of an abbreviated application, we do not propose changing this policy or providing new or similar forms of exclusivity to non-orphan biologics.

## C. FDA/SPONSOR MEETINGS

**Issue:**

The FDA recently issued a draft guidance on Formal Meetings with Sponsors and Applicants for PDUFA products that addresses the timely and effective conduct of meetings with the FDA. The MBC is pleased that FDAMA implementation is going forward, and that this guidance addresses many comments raised in our White Paper. There are, however, two outstanding issues not addressed by the guidance. The FDA has not indicated specific time lines regarding dispute resolutions and fast track sponsor/FDA meetings.

**Proposal:**

Regarding dispute resolution, we suggested in our White Paper that the sponsor should provide corrections to the FDA within 15 days of receiving the minutes from the agency, with the FDA response coming within 15 days of receipt of corrections. Further, we called for the FDA to rule on any disagreements resulting from this process within 30 calendar days from the date of sponsor appeal. The recent guidance document on meetings talks about proper procedures for dispute resolution, but sets no firm timelines for either agency response to minutes clarification or the appeals process.

On the fast track issue, we have proposed that meetings always take place within 30 days of receipt of the sponsor's request, with actual scheduling of meetings to be made within 14 days of the request. These timeframes we believe are consistent with other efforts to accelerate the approval of fast track products and recognizes the importance of this objective under FDAMA. The draft guidance, however, makes no provisions for fast track meetings. The MBC desires to see established, firm timelines for dispute resolution and fast track meetings, and raises this issue in light of the present guidance, which currently is in draft form and open to comment and suggestion.

## D. GENERIC TYPE APPROVAL SYSTEMS

**Issue:**

Recombinant proteins should not be subject to generic-type approval systems, regardless of whether such products are regulated as "drugs" or "biological products"

The biotech industry strongly agrees with Commissioner Henney's statements that "biological products" should not be subject to generic-type approval systems under current law.[7] We are concerned, however, with recent CDER activities to encourage generic drug companies to submit "paper NDAs" for recombinant protein therapeutics

[7] Commissioner Henney made this statement in response to written questions submitted to her by the Senate committee that conducted her confirmation hearing and reaffirmed it at a meeting with the Massachusetts Biotechnology Council on April 1, 1999.

that are regulated as "drugs."[8] Under the Intercenter Agreement between CDER and CBER, FDA generally determines whether to regulate a recombinant protein as a drug or biologic based on such non-scientific criteria as administrative efficiency and historical precedent. But public health considerations -- as well as the need for consistency between the Centers with respect to approval requirements for macromolecular products -- should preclude CDER from creating generic-type approval systems for recombinant protein products that are regulated as drugs.

**Background:**

Since 1984, the Food, Drug and Cosmetic (FDC) Act – but not the Public Health Service (PHS) Act – has authorized FDA to approve generic drug applications.[9] A generic drug must be the "same" as the innovator drug to be approvable. No generic drug may be approved prior to the expiration of any market exclusivity period provided to the sponsor of the innovator drug.[10] Nor may a generic drug be approved during the term of a patent on the innovator drug (or the patented use for which approval is sought), including any patent term extension.[11] Innovator drug sponsors who believe their patent(s) would be infringed by a generic drug may prevent FDA from approving the generic product during the course of patent litigation against the generic sponsor. Upon approval, generic drugs are assigned therapeutic equivalence ratings that, in most cases, permit generic substitution under most States' laws. None of these provisions has ever been applied to recombinant proteins, regardless of whether they were regulated as "drugs" or "biological products."

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[8] In 1998, CDER established a "Complex Drug Substances Coordinating Committee" to facilitate generic approval of various "complex" products, including recombinant proteins, monoclonal antibodies, and other large molecules. According to *Health News Daily*, CDER's Roger Williams recently told the Generic Pharmaceutical Industry Association that CDER would welcome the receipt of "paper NDAs," submitted under section 505(b)(2), for recombinant proteins regulated by that Center and that such products would be deemed therapeutically equivalent for purposes of generic substitution.

[9] "Drugs" are regulated under the FDC Act, while "biological products are regulated under the PHS Act. In 1984, the FDC Act was amended to create two new types of drug applications – abbreviated new drug applications (ANDAs) and "paper NDAs" – that reference the clinical trial data generated by another company in support of an NDA for the original (reference) version of a product. This paper's use of the phrase "generic drugs" refers to both ANDAs and "paper NDAs," except as otherwise noted.

[10] FDA may not approve any ANDA or paper NDA that references: (a) an original NDA for a new chemical entity (NCE) that was approved during the preceding five year period or (b) a supplemental NDA (sNDA) for either a new indication or new formulation that was approved during the preceding three year period.

[11] An ANDA or "paper NDA" application must contain a patent certification with respect to the referenced NDA drug. If the *Orange Book* lists a patent for the NDA product and/or its only approved use, the generic drug applicant must either agree that his product will not be eligible for approval until the patent expires or challenge the patent's validity or applicability to the generic product. A generic drug applicant who challenges a listed patent must notify the NDA holder of this fact; if the NDA holder then files a patent infringement suit within the prescribed time, FDA may not approve the generic until 30 months later (assuming that the patent is still unexpired on such date and that no final court decision has been rendered).

**Discussion:**

The biotechnology industry believes that, in the absence of comparative clinical trials, there are compelling scientific reasons for requiring that two molecules be structurally and functionally identical before concluding that clinical trials performed on the first molecule can be relied upon to approve the second molecule and provide for routine substitution between the two. [12]

Small molecules with simple structures (such as most "drugs") are far easier to replicate than large molecules with complex structures (such as most "biological products"). Where two molecules are indistinguishable in size, weight, composition, and structure, bioequivalence studies confirming "sameness" are generally adequate. But the current state of the art does not permit one to predict when minor differences in size, weight, composition, and/or structure will alter the clinical profile of a product, and when it will not, especially when the two products are manufactured by different sponsors using different manufacturing techniques.[13] In some cases, relatively minor differences in the carbohydrate structures of two otherwise-identical glycoproteins will result in significantly different therapeutic effects.[14]

Whether a product is regulated as a drug or a biologic is irrelevant in evaluating the clinical significance of small variations between molecules. Yet it appears that CDER may be prepared to use the mere fact that a molecule is regulated as a drug as the basis for characterizing similar-but-not-identical molecules as therapeutically equivalent and substitutable, even when the products have never been evaluated in comparative studies.

CDER's jurisdiction over some biotech products is derived from a 1991 "Intercenter Agreement" between CDER and CBER allocating jurisdiction between the two based on an apparently simple concept: "A product class is defined as a distinct category of agents recognizable by physical characteristics, source materials or pharmacologic properties."

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[12] Note that whether two drugs/biologics are considered to be the "same" depends on the context. Public health considerations appropriately place the burden of proof on the generic drug sponsor to demonstrate that its product is identical to the earlier (reference) drug on which safety and efficacy trials were conducted, since generic approval will result in routine substitution without physician consultation. By contrast, orphan drug regulations place the burden of proof on the sponsor of a recombinant protein to show that minor differences between its product and an approved product demonstrate clinical superiority (or other compelling public health reasons) justifying a breach of the earlier product's unexpired market exclusivity. Both cases recognize that it is impossible to tell whether minor differences between molecules will produce clinical differences without comparative trials and presume that almost-identical products are either the same – or are not the same – depending on the nature of the public health interest that this determination will affect.

[13] Manufacturing techniques are generally maintained as trade secrets. It is highly improbably that competing manufacturers making recombinant proteins will be using identical materials and processes, or that their products will be structurally identical. Functional equivalence may nevertheless be accomplished, but cannot reasonably be presumed in the absence of appropriate clinical data.

[14] For example, the clinical effectiveness of natural glucocerebrosidase (GCR) was substantially enhanced through modification of the molecule's carbohydrate structure to allow preferential targeting of macrophage cells. CDER approved an NDA for Ceredase, the modified enzyme, in 1991 and Cerezyme, a recombinant analogue of the modified enzyme, in 1994.

Unfortunately, the simplicity of this concept is belied by the elaborate, and often inconsistent, scheme described in the Agreement. For example:

- In some cases, manufacturing method is determinative. Polynucleotide products – including products complementary to RNA or DNA sequences – are regulated as drugs if they are chemically synthesized, but as biologics if they are biologically synthesized.

- In other cases, manufacturing method is irrelevant. Hormones and antibiotics are regulated as drugs, regardless of molecular structure or method of synthesis, while allergenic products and vaccines are regulated as biologics, regardless of molecular structure or method of synthesis.

- Products from similar source materials are sometimes regulated differently. Human tissue-derived products are regulated as drugs, while human blood-derived products are regulated as biologics. This rule appears to be derived from CBER's historical authority over blood and blood products, rather than any evidence that a protein that was extracted from tissue is vastly different from the same protein derived from blood.

- General principles do not always have general applicability. Several classes of products that are regulated as drugs contain subclasses that are regulated as biologics, and vice versa. For example, the rule that all hormones (including recombinant proteins) be regulated as drugs was not applied to recombinant erythropoietin (EPO), which is regulated as a biologic.[15] And the general rule that all non-hormone recombinant proteins be regulated as biologics was not applied to recombinant glucocerebrosidase (GCR).[16]

- Radioactivity counts. Biologics that are combined with radioactive components are regulated as biologics, but those that are combined with non-radioactive components are regulated as drugs.

- Drug/biologic combinations are regulated based on FDA's determination of the primary mode of action. If the biological component enhances efficacy or reduces toxicity of the drug component, the product will be regulated as a drug, but if the drug component enhances efficacy or reduces toxicity of the biological component, the product will be regulated as a biologic.

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[15] FDA's decision to regulate EPO as a biologic predated the Intercenter Agreement, but illustrate the apparently arbitrary way in which the Agency sometime makes jurisdictional decisions than may have profound consequences.

[16] Under the Intercenter Agreement, recombinant GCR would have been regulated as a biologic, rather than as a drug, had a tissue-derived version of the enzyme – regulated by CDER -- not been developed first. Recombinant products for similar lysosomal storage disorders are regulated as biologics because there are no naturally-derived (i.e., CDER-approved) versions of these products.

- Administrative convenience. FDA explicitly reserves the right to transfer responsibility for a product from one Center to the other "for scientific or administrative reasons."

The industry recognizes FDA's legitimate interest in achieving efficiency in its product reviews. However, administrative concerns should never trump public health interests or produce inconsistency in the regulation of similar products. The state of the art demonstrates that different glycoforms of the same recombinant protein *sometimes* possess different clinical profiles. Given this situation, FDA should not allow a different glycoform to receive a generic-type approval, regardless of whether the reference product is regulated as a drug or a biologic.

## CONCLUDING COMMENTS

The MBC as always appreciates the opportunity to interact with the FDA. We trust that our comments are given due consideration by Agency policy makers, and indeed there is ample evidence that views put forth during an earlier stakeholders conference and in such correspondence as the MBC's FDAMA White Paper have been heard and have made a difference.

In the spirit of enhanced communications, then, we anticipate receiving feedback from the FDA on issues raised in this paper. Some matters no doubt can be taken care of with brief memos, but others will require more comprehensive review. We look forward to receiving all of the above.

U.S.C. 1905, the submissions may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sec. 505 (21 U.S.C. 355)) and under authority delegated to the Director of the Center for Drug Evaluation and Research (21 CFR 5.82).

Dated: March 3, 1999.

**Janet Woodcock,**

*Director, Center for Drug Evaluation and Research.*

[FR Doc. 99-6808 Filed 3-19-99; 8:45 am]

BILLING CODE 4160-01-F

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. 99N-0386]**

### Talking With Stakeholders About FDA Modernization; Notice of Meetings and Teleconference

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice of meetings and teleconference.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing public meetings and an interactive satellite teleconference entitled "Talking With Stakeholders About FDA Modernization." The purpose of the meeting is to discuss the agency's progress in implementing the FDA Modernization Act (FDAMA) and to seek additional input on specific FDAMA performance targets.

**DATES:** The meetings and teleconference will be held on April 28, 1999. The deadlines for speaker registration and attendance registration are April 9, 1999, and April 16, 1999, respectively. Stakeholders interested in being a member of the studio audience should indicate their interest by April 15, 1999. Comments may be submitted by May 14, 1999. For additional information regarding registration, the meetings, and teleconference, see Table 1 in section III of this document.

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, e-mail "FDADockets@bangate.fda.gov", or via the FDA web site "http://www.fda.gov".

**FOR FURTHER INFORMATION CONTACT:** Carrie Smith Hanley, Office of External Affairs (HF-60), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-3365, FAX: 301-594-0113, e-mail: "chanley@oc.fda.gov".

**SUPPLEMENTARY INFORMATION:**

#### I. Background

Section 406(b) of FDAMA (21 U.S.C. 393(f) and (g)) requires the agency: To consult with its external stakeholders as it moves forward to modernize the agency; to develop a plan, based on input from stakeholders, for complying with the agency's obligations under the Federal Food, Drug, and Cosmetic Act (the act); and to periodically revisit the plan in consultation with stakeholders to make appropriate adjustments. As a culmination of these requirements, FDA will issue a performance report to Congress at the end of the 1999 calendar year.

A summary of the agency's responses to each obligation follows.

*A. Consult With External Stakeholders*

To respond to the first requirement of section 406(b) of FDAMA, the agency held a series of well attended public meetings last summer to obtain stakeholder views on how FDA can best meet its statutory obligations. Stakeholders offered a wealth of productive suggestions, many of which reflect their desire for greater involvement in FDA's work by contributing to the agency's future strategies and for receiving clear and timely information about the agency's processes and new regulated products.

*B. Develop a Plan That Reflects Stakeholders Views*

FDA listened carefully to its stakeholders and used their contributions to guide the development of a plan for complying with its obligations under FDAMA, as well as responding to the public's expectations. In the **Federal Register** of November 24, 1998 (63 FR 65000), the agency published the "FDA Plan for Statutory Compliance" (see FDA's web site, "http://www.fda.gov/oc/fdama/fdamapln"). This plan provides a broad, agency wide strategic framework and specific performance goals for the current fiscal year (1999) that will allow FDA to act on stakeholder recommendations as well as allow the agency to meet its statutory obligations. The strategic framework outlines six broad directions: Strengthening the science base, closely collaborating with stakeholders, establishing risk-based priorities, adopting a systems approach, continuing to reengineer FDA processes, and capitalizing on information technology. The plan describes how the agency is already implementing many strategies in new and creative ways within each of these broad directions.

*C. Periodically Revisit the Plan in Consultation with Stakeholders*

FDA is now preparing to revisit the 406(b) plan as part of a formal consultation with its stakeholders on April 28, 1999. The agency would like to receive input from stakeholders on the elements of the plan that have been implemented thus far and obtain additional suggestions on how the agency can continue to improve its modernization efforts. FDA specifically wants input on how to: (1) Strengthen its science base and (2) improve its communication processes. To help focus the discussion at the April 28, 1999, meeting, FDA has designed five questions that address these two concerns. As stakeholders respond to these questions, it may be useful to review the "FDA Plan for Statutory Compliance" which outlines the agency's current and proposed activities in these two areas. FDA requests that stakeholders address the five questions below in their oral and/or written views:

1. Science based decisions are made throughout the life span of products from initial research, development and testing, through production, marketing, and consumption. These decisions require the best science to identify, evaluate, and balance product risks and benefits. It is crucial that FDA, in collaboration with product sponsors, develop a shared understanding of new science and technologies and their effect throughout a product's life span.

What actions do you propose the agency take to expand FDA's capability to incorporate state-of-the-art science into its risk-based decisionmaking?

2. As the agency attempts to meet its public health responsibilities, the speed of discovery results in an avalanche of new information from government, academic, and industry scientists.

What actions do you propose to facilitate the exchange and integration of scientific information to better enable FDA to meet its public health responsibilities throughout a product's lifecycle?

3. Most products in the American marketplace, especially medical ones, have two facets. On one side they benefit users and often improve lives. They are, however, rarely without risk, and their use can result in known and unknown side effects. Consumers must weigh benefits and risks before using these products, oftentimes with incomplete information.

What actions do you propose for educating the public about the concept

of balancing risks against benefits in public health decisionmaking?

4. The agency stated in the "FDA Plan for Statutory Compliance" that inflation has eroded real assets that can be applied to meet its public health mission while Congress has increased its responsibilities.

Because the agency must allocate its limited resources to achieve the greatest impact, what actions do you propose to enable FDA and its product centers to focus resources on areas of greatest risk to the public health?

5. FDAMA requires the agency to continue to meet with stakeholders on key issues. Meetings have ranged from explaining the positions of the agency on particular issues to working with sponsors on product applications. Historically, these interactions have benefited both stakeholders, through better knowledge of FDA, and the agency, by leading to positive changes in its operations.

Because the agency wants to assure that its stakeholders are aware of and participate in its modernization activities, what additional actions do you propose for enhancing communication processes that allow for ongoing feedback and/or evaluation of our modernization efforts?

## II. Comments

Stakeholders are encouraged to submit their responses in advance of the April 28, 1999, meeting. Written comments should be identified with docket number 99N-0386 and submitted to the Dockets Management Branch (address above). In order to promote a variety of responses, stakeholders are encouraged to state a proposed action as a separate concise statement followed by a written explanation of its meaning.

## III. Scheduled Meetings

Open public meetings with stakeholders will be held in several locations throughout the country. These meetings will provide down-link interactive viewing sites for the live satellite teleconference and also provide an opportunity for formal presentations to FDA's senior managers at the local meetings. The teleconference will feature Jane E. Henney, Commissioner of Food and Drugs, and Linda A. Suydam, Associate Commissioner for Strategic Management, who will be talking with stakeholders during the live satellite teleconference. These meetings are open to all stakeholders and will be co-hosted by FDA's field offices and centers, and they will focus on the specific product center listed in the first column of Table 1 of this document. The scheduled time of meetings, as listed in Table 1 of this document, includes the time devoted to the live satellite teleconference broadcast, as well as a period of time for presentations and/or discussion of the questions listed in section I.C of this document.

TABLE 1

| Center/City Registration | Location/Address | Scheduled Time Of Meeting | Speaker Registration Contact | Attendance Contact |
|---|---|---|---|---|
| Center for Drug Evaluation and Research, Philadelphia, PA | Temple University, Main Campus, Ritter Hall, Kiva Auditorium, 130 Cecil B. Moore Ave., Philadelphia, PA | 12:30 p.m. to 6 p.m. Eastern Time | Marcia Trenter, Phone: 301-827-1492, Fax: 301-827-3056, Email: Trenterm@cder.fda.gov | Anitra Brown-Reed, Phone: 215-597-4390 ext. 4202, Fax: 215-597-4660, Email: Abrown2@ora.fda.gov |
| Center for Biologics Evaluation and Research, Boston, MA | Boston University, School of Medicine, 715 Albany St., Boston, MA | 9:30 a.m. to 3 p.m. Eastern Time | Lorrie Harrison, Phone: 301-827-5546, Fax: 301-827-3079, Email: Harrison@cber.fda.gov | Lorrie Harrison, Phone: 301-827-5546, Fax: 301-827-3079, Email: Harrison@cber.fda.gov |
| Center for Biologics Evaluation and Research, San Francisco, CA | South San Francisco Conference Ctr., 255 South Airport Blvd., South San Francisco, CA | 9:30 a.m. to 3 p.m. Pacific Time | Lorrie Harrison, Phone: 301-827-5546, Fax: 301-827-3079, Email: Harrison@cber.fda.gov | Lorrie Harrison, Phone: 301-827-5546, Fax: 301-827-3079, Email: Harrison@cber.fda.gov |
| Center for Food Safety and Applied Nutrition, Chicago, IL | Ralph Metcalfe Federal Bldg., 77 West Jackson Blvd., Morrison Conference Room, Chicago, IL | 12 Noon to 4:30 p.m. Central Time | Marquita Steadman, Phone: 301-827-6735, Fax: 301-480-5730, Email: msteadman@bangate.fda.gov | Kimberly Phillips, Phone: 312-353-7126 ext. 193, Fax: 312-886-3280, Email: Kphillip@ora.fda.gov |
| Center for Veterinary Medicine, Overland Park, KS | Johnson County Community College, Bldg. CE, rm. 211, 12345 College Blvd., (Kansas City, KS) (111th & Quivera), Overland Park, Kansas (Kansas City, KS) | 11:30 a.m. to 5 p.m. Central Time | Linda Grassie, Phone: 301-827-6513, Fax: 301-594-1831, Email: Lgrassie@bangate.fda.gov | Linda Grassie, Phone: 301-827-6513, Fax: 301-594-1831, Email: Lgrassie@bangate.fda.gov |
| Center for Devices and Radiological Health, San Diego, CA | Scripps Research Institute, Shepherd Great Hall, Schaetzle Education Center, Scripps Memorial Hospital, 9890 Genesee Ave., La Jolla, CA, (San Diego) | 9:45 a.m. to 4 p.m. Pacific Time | Ron Jans, Phone: 301-827-0048, Fax: 301-443-8810, Email: Rsj@cdrh.fda.gov | Ron Jans, Phone: 301-827-0048, Fax: 301-443-8810, Email: Rsj@cdrh.fda.gov |

TABLE 1—Continued

| Center/City Registration | Location/Address | Scheduled Time Of Meeting | Speaker Registration Contact | Attendance Contact |
|---|---|---|---|---|
| Office of Regulatory Affairs, Atlanta, GA | Food and Drug Administration, 60 Eighth St., N.E. Atlanta, GA | 12 noon to 5 p.m. Eastern Time | Joann Pittman, Phone: 404–253–1272, Fax: 404–253–1202, Email: jpittman@ora.fda.gov | Joann Pittman, Phone: 404–253–1272, Fax: 404–253–1202, Email: jpittman@ora.fda.gov |
| FDA General, Washington, DC | United States Department of Agriculture, Jefferson Auditorium (West Wing), 14th and Independence Ave., SW., Washington, DC | 12:30 p.m. to 5:30 p.m. Eastern Time | Mary Gross, Phone: 301–827–3364, Fax: 301–594–0113, Email: mgross@oc.fda.gov | Russell Campbell, Phone: 301–827–4413, Fax: 301–443–9767, Email: rcampbe2@oc.fda.gov |

A separate FDAMA section on the FDA web site will provide current information about these public meetings. It is highly recommended that individuals who wish to participate at these public meetings plan to attend the entire session. Each public meeting will include an opportunity for an open comment session where attendees can express their views.

The interactive satellite teleconference is a C-Band broadcast with the following coordinates: satellite GE–2, 85 West, Transponder 3, frequency 3760 MHz Vertical. Test signal begins at 12 noon Eastern Time. The satellite teleconference will begin promptly at 1 p.m. Eastern Time and end no later than 3:30 p.m. Eastern Time. Limited seating will be available for a live studio audience at the broadcast studio in Gaithersburg, MD. Individuals representing broad interest groups are invited to participate in the studio audience. A balanced representation of FDA stakeholders will be selected. Stakeholders who are interested in participating in the broadcast as a member of the studio audience should indicate their interest by April 15, 1999, to Carrie Smith Hanley, Office of External Affairs at the phone, fax or e-mail address listed in the section of this document entitled "**For Further Information Contact**".

## IV. Registration and Requests for Oral Presentations

All participants should send registration information (including name, title, firm name, address, telephone and fax number) to the appropriate "attendance registration" contact person listed in section III of this document by April 16, 1999. If you need special accommodations due to a disability, please indicate such at the time of registration.

Participants who wish to make a formal oral presentation should register with the appropriate contact for "speaker registration" identified by meeting in section III of this document by April 9, 1999. Formal oral presentations will not be made at the studio. Stakeholders wishing to make presentations should make their wishes known to the appropriate individuals listed in section III of this document.

## V. Transcripts

Transcripts of the meetings (from each site listed in section III of this document) may be requested in writing from the Freedom of Information Office (HFI–35), Food and Drug Administration, 5600 Fishers Lane, rm. 12A–16, Rockville MD 20857, approximately 15 working days after the meeting at a cost of 10 cents per page. The transcript of the meeting will be available for public examination at the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday, as well as on the FDA web site "http://www.fda.gov".

Dated: March 17, 1999.

**William K. Hubbard,**

*Acting Deputy Commissioner for Policy.*

[FR Doc. 99–7038 Filed 3–18–99; 11:48 am]

BILLING CODE 4160–01–F

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Health Resources and Services Administration

### Council on Graduate Medical Education Meeting

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), announcement is made of the following National Advisory body scheduled to meet during the month of April 1999:

*Name:* Council on Graduate Medical Education.

*Date and Time:* April 14, 1999, 8:30 a.m.—5:15 p.m. April 15, 1999, 8:30 a.m.—12 p.m.

*Place:* Washington Plaza, 10 Thomas Circle, N.W., Massachusetts Avenue & 14th Street, Washington, D.C.

This meeting is open to the public.

*Agenda:* The agenda will include: Welcome and opening comments from the Administrator, Health Resources and Services Administration, the Associate Administrator for Health Professions and the Acting Executive Secretary of COGME; a panel on Ambulatory Settings, the Changing Environment, and Accreditation and Certification in GME; a panel on GME Physician Workforce Assessment Activities; and a panel on The Physician Public Health Workforce. The Council will hear the reports of its work groups on Ambulatory Programs and Financing, and Physician Workforce. The Council will also hear an update on Legislative Proposals and Activities. It will discuss the COGME 15th Report outline and its future direction.

Anyone requiring information regarding the subject should contact Stanford M. Bastacky, D.M.D., M.H.S.A., Executive Secretary, telephone (301) 443–6326, Council on Graduate Medical Education, Division of Medicine, Bureau of Health Professions, Room 9A–27, Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20857.

Agenda items are subject to change as priorities dictate.

Dated: March 16, 1999.

**Jane M. Harrison,**

*Director, Division of Policy Review and Coordination.*

[FR Doc. 99–6809 Filed 3–19–99; 8:45 am]

BILLING CODE 4160–15–P

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Substance Abuse and Mental Health Services Administration

### Agency Information Collection Activities: Proposed Collection; Comment Request

In compliance with Section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995 concerning opportunity for public comment on proposed collections of information, the Substance Abuse and Mental Health

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

MAR 23 1999

Dear Colleague:

The Center for Biologics Evaluation and Research (CBER) and the Office of Regulatory Affairs (ORA) are cohosting two open public meetings to solicit views and comments on how the Food and Drug Administration (FDA) can best meet its statutory obligations under the Food, Drug and Cosmetic Act as amended by the FDA Modernization Act (FDAMA) of 1997. These two public meetings have identical content and are scheduled as follows:

| | |
|---|---|
| **Date and Time:** | April 28, 1999, 9:30am to 3:30pm (Eastern time) |
| **Location:** | Boston University<br>School of Medicine<br>715 Albany Street<br>Boston, MA 02118 |
| **Date and Time:** | April 28, 1999, 9:30am to 3:00pm (Pacific time) |
| **Location:** | South San Francisco Conference Center<br>255 South Airport Boulevard<br>South San Francisco, CA 94080 |

Section 406(b) of the FDAMA requires the Agency to consult with its external stakeholders, specifically "appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry." These meetings will include: (1) a live satellite teleconference with Jane E. Henney, M.D., Commissioner of Food and Drugs, and Linda A. Suydam, D.P.A., Associate Commissioner for Strategic Management, entitled, "Talking with Stakeholders about FDA Modernization" to discuss FDA's progress in implementing FDAMA and to seek additional input on specific FDAMA performance targets; and (2) a CBER-specific meeting at which stakeholders can present their views to senior Center management regarding CBER's performance under the Act. I will cohost the CBER-specific portion of the event in South San Francisco with Patricia Ziobro, District Director, San Francisco District Office, and Mark Elengold, Deputy Director (Operations), CBER, will cohost the meeting in Boston with John Marzilli, District Director, New England District Office.

FDA met with its stakeholders through a series of meetings in August and September 1998 to solicit public input on how the Agency can meet its statutory obligations. On November 21, 1998, the Agency published The FDA Plan for Statutory Compliance (see FDA's web site, http://www.fda.gov/oc/fdama/fdamapln), which provides the framework and specific performance goals for fiscal year 1999.

The Agency is now entering the second cycle of its formal dialogue with stakeholders on April 28, 1999. Two underlying themes are the focus of this dialogue: (1) strengthening FDA's science base and setting risk-based priorities, and (2) improving communication processes with the public. To help focus discussion, FDA is requesting that stakeholders address the five questions listed below in their oral/written responses as to how the Agency can best strengthen its science base and improve communication with stakeholders:

1. What actions do you propose the Agency take to expand FDA's capability to incorporate state-of-the-art science into its risk-based decision making?
2. What actions do you propose to facilitate the exchange and integration of scientific information to better enable FDA to meet its public health responsibilities throughout a product's life cycle?

3. What actions do you propose for educating the public about the concept of balancing risks against benefits in public health decision making?
4. What actions do you propose to enable FDA and its product centers to focus resources on areas of greatest risk to the public health?
5. What actions do you propose for enhancing communication processes that allow for ongoing feedback and/or evaluation of our modernization efforts?

The Agency has established a docket to receive any ideas you may wish to propose. Comments may be submitted in writing to Docket No. 99N-0386 until April 14, 1999, at the following address: Dockets Management Branch, Food and Drug Administration, Room 1061, HFA-305, 5600 Fishers Lane, Rockville, MD 20857.

This public meeting is free of charge; however, due to space limitations, early registration is recommended. If you wish to attend the meeting, please submit your name, affiliation and which location you would like to attend via facsimile or e-mail to: Lorrie Harrison, phone 301-827-5546, FAX 301-827-3843, e-mail harrison@cber.fda.gov. Additional information may be found at the Agency's website at http://www.fda.gov. If you would like to make a presentation, please send your name, title, affiliation, street address, e-mail address and telephone and fax numbers, along with a short description of the topic you wish to address, to Ms. Harrison. The deadline for receiving requests to speak is Friday, April 9, 1999. Each person who submits a request will receive a response by April 16, 1999, stating whether they have been included in the program.

I look forward to hearing your views and suggestions on how we can continue to implement FDAMA. We are committed to carrying out these consultations in a spirit of candor and cooperation. If you have any questions, please contact Dennis Strickland at 301-827-2000.

Sincerely,

Kathryn C. Zoon, Ph.D.
Director
Center for Biologics Evaluation
and Research

Enclosures

**1. Science based decisions are made throughout the life span of products from initial research, development and testing, through production, marketing, and consumption. These decisions require the best science to identify, evaluate, and balance product risks and benefits. It is crucial that FDA, in collaboration with product sponsors, develop a shared understanding of new science and technologies and their effect throughout a product's life span.**

**What actions do you propose the agency take to expand FDA's capability to incorporate state-of-the-art science into its risk-based decision making?**

**2. As the agency attempts to meet its public health responsibilities, the speed of discovery results in an avalanche of new information from government, academic, and industry scientists.**

**What actions do you propose to facilitate the exchange and integration of scientific information to better enable FDA to meet its public health responsibilities throughout a product's lifecycle?**

**3. Most products in the American marketplace, especially medical ones, have two facets. On one side they benefit users and often improve lives. They are, however, rarely without risk, and their use can result in known and unknown side effects. Consumers must weigh benefits and risks before using these products, often times with incomplete information.**

**What actions do you propose for educating the public about the concept of balancing risks against benefits in public health decision making?**

**4. The agency stated in the "FDA Plan for Statutory Compliance" that inflation has eroded real assets that can be applied to meet its public health mission while Congress has increased its responsibilities.**

**Because the agency must allocate its limited resources to achieve the greatest impact, what actions do you propose to enable FDA and its product centers to focus resources on areas of greatest risk to the public health?**

**5. FDAMA requires the agency to continue to meet with stakeholders on key issues. Meetings have ranged from explaining the positions of the agency on particular issues to working with sponsors on product applications. Historically, these interactions have benefited both stakeholders, through better knowledge of FDA, and the agency, by leading to positive changes in its operations.**

**Because the agency wants to assure that its stakeholders are aware of and participate in its modernization activities, what additional actions do you propose for enhancing communication processes that allow for ongoing feedback and/or evaluation of our modernization efforts?**

# DISCUSSION QUESTIONS FOR COMMISSIONER HENNEY
# APRIL 1, 1999

**I. Intro and brief overview of issues we would like to address and purpose of the creation of MBC white paper** **J. Bourque**

**II. Discussion questions**

**1. FDAMA Implementation-MBC White Paper**

**Point 1: FDA meetings, user fees and performance goals:** **leader?**

Developing companies need to efficiently plan and manage resources. Often a company will meet with the FDA and reach a verbal agreement on acceptability of protocol, design of trial, timelines, etc. Then the reviewer will change and will state that the documentation regarding agreement is unclear and that the approach is not acceptable. The process must be restarted again. When a company submits minutes of a meeting for FDA concurrence, the FDA often does not comment on the minutes of the meeting in a timely manner. The company is left to either assume the understanding is correct and risk disagreement later; wait an indefinite period of time for the FDA to comment, or risk irritating the reviewer with repeated inquiries as to the status of the minutes.

**The FDA is preparing Guidance on these issues and there is no deadline set. The MBC would like your comments on establishing firm timelines for:**

- **requesting and scheduling meetings, filing proposed agendas, drafting and approving meeting minutes**
- **specific review deadlines for initial marketing applications and efficacy and manufacturing supplements.**

**Point 2: Pharmacoeconomics** **leader?**

Managed care or other provider organizations are demanding studies that will demonstration how use of a particular drug will effect overall health care costs. It is important to provide competent and reliable scientific evidence standards to pharmacoeconomic studies. FDAMA necessitates a new approach by FDA for review of promotional material involving health costs economic information following FTC standards. This permits the promotional dissemination of health care economic information on costs assigned to outcomes not only from adequate and well controlled trials but to encompass outcomes and costs collected outside of these trials but still directly elated to the labeled indication.

**Please give us your views on the FDA use of FTC standards to guide the dissemination of health care economic information.**

**2. Advisory Panel System** **Richard Pops**

**Point 1**: Companies regulated as biologics under CBER are given the opportunity to review and comment on FDA's draft panel documents before they are sent to the advisory panel whereas under CDER, companies are rarely given that opportunity. CBER's procedure allows further interaction, clarification and discussion with the FDA prior to the advisory panel meeting thus freeing the advisory panel to focus on areas of genuine concern or disagreement. We would like all companies to be offered that opportunity.

- **Would you support such harmonization of good policy practices between CBER and CDER?**

**Point 2**: The original role of the advisory panel was to provide a 3rd party evaluation mechanism for scientific controversies. The industry is concerned that the advisory panels are being used more often than is necessary. The advisory panel meeting can impact a companies ability to raise research dollars as well as cause a 20-30% decrease in stock prices even when the product is recommended for approval.

- **Would you support the Agency moving to a rapid approval rather than an Advisory Panel meeting if a company has demonstrated safety and efficacy?**

**3. Generic biologics:** **Alison Taunton-Rigby**

You have stated that you would not create a generic biologics program at FDA.

- **Do you think it could be interpreted that biological products regulated by CDER – such as recombinant proteins – would be available for a generics program versus "biologics" regulated by CBER?**
- **How would you clarify such a misinterpretation?**

**4. Pediatrics** **Leader?**

The biotech industry recognizes the need for pediatric studies but is concerned that it will be required for all drugs and biologics unless companies can demonstrate that such a study is inappropriate. The burden on small companies that are not profitable is clear. However, "drugs" are eligible for the additional 6 months of market exclusivity whereas "biologics" are not. While we do not want to create a Hatch-Waxman type process which could imply the creation of a "generics biologics approval process", we would like to see this incentive offered to both drugs and biologics.

- **Would you be willing to support or propose legislation that would allow companies pediatric extensions of their unexpired orphan drug market exclusivity regardless of whether the product is regulated as a drug or biologic?**

**III. Closing Comments** **Janice Bourque**

We would like to thank both of you for your time today. We appreciate the opportunity to speak candidly with you about issues of concern to the Massachusetts biotech community.

The MBC would like to continue to be of service to the FDA. Massachusetts Biotechnology companies are at the cutting edge of new technologies. The local FDA office and the MBC received the Hammer Award from Vice President Al Gore for its pre-inspection model program

Perhaps we could develop a model program that offers seminars for the FDA on cutting edge technology in a local facility (such as the University of Massachusetts Biologics Laboratory in Jamaica Plain that the FDA and the CDC already utilize). The FDA could perhaps offer guidance seminars for small growing companies on how to improve the reporting, interactions, and discussions with the FDA.

We would like to continue this dialogue and schedule a follow up meeting in Washington to discuss these matters further. Is there a point person we could contact to arrange such meetings? We look forward to meeting again soon. Thank you.

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